MEMORANDUM

Date: September 22, 2005

To: Psychopharmacologic Drugs Advisory Committee and Guests

From: Vanda Pharmaceuticals Inc.

Subject: Briefing document for trial design of long term efficacy of antipsychotics for the treatment of schizophrenia

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Introduction

The two most commonly employed designs for adequate, well-controlled assessments of long-term antipsychotic effectiveness are placebo control and active control non-inferiority (hereafter referred to as active control). The advantage of placebo-controlled studies is assay sensitivity, or the ability of this study type to detect a treatment difference (1, 2). Active control designs are frequently criticized because they are thought to lack assay sensitivity: if the test drug is found to be non-inferior to the active control it is more challenging to deduce whether both drugs worked (and would have separated from placebo, had one been included in the study), or both failed (in which case neither would have separated from placebo). The active control design can only be considered valid if it can be assumed that the active control will separate from placebo.

The ICH E10 Guidance (3) advises that assay sensitivity can be deduced from historical evidence available from similarly designed trials as long as these studies meet two conditions. **The first condition is that the active drug must consistently separate from placebo**. If this is not the case, if the active drug failed to separate from placebo in a number of adequately designed and conducted trials, then the non-inferiority design is not valid. **The second condition is that the margin of separation must not be larger than the difference between the active control drug and placebo** (4-6). This document argues that there is sufficient historical data to determine that (1) antipsychotics consistently separate from placebo in studies of long-term effectiveness, and (2) the margin of separation between antipsychotics and placebo is large and quantifiable.

Finally, this document will comment on the stabilization period in long-term designs.

I. Validation of Non-Inferiority Trial Design for Assessment of Long-Term Antipsychotic Effectiveness

Antipsychotics Consistently Separate from Placebo

Six studies of the long-term effectiveness of antipsychotics have been identified that utilized a placebo-control. These studies were found in the literature (7-12) or were available from the FDA through freedom of information and involved haloperidol, ziprasidone, olanzapine and aripiprazole. Each study was similarly designed and executed: efficacy was assessed by prevention of relapse or impending relapse, as defined by significant increases in the PANSS or CGI scores. Studies A and E in Table 1 utilized a stabilization period (range = 8-15 weeks). Studies B, C, and F did not include a stability period. Endpoints were either at 6 months (26-28 weeks) or 12 months (46-52 weeks).

The data presented in Table 1 demonstrate that the rate of relapse for active treatment consistently separated from placebo treatment. Though data were not available to calculate Cohen's *d'* as a measurement of the margin of separation between active and placebo, relapse rates were significantly different for active and placebo arms. Mean relapse rate for placebo was 72% (range = 69-77%) and 58% (range = 55-63%) for studies of 12 and 6 month duration, respectively. Mean relapse rate for active treatments was 33% (range = 11-41%) and 29% (range = 6-39%) for studies of 12 and 6 months duration, respectively. The mean difference between active and placebo was 40% (30-58%) and 27% (21-49%) for 12- and 6-month studies, respectively. These data support the conclusion that in long-term recurrence prevention studies, antipsychotics separate consistently from placebo.

Table 1: Review of atypical antipsychotic vs. placebo percent of relapse and calculated delta values

	Study	Endpoint	Dose (mg)	Percent of Relapse			source
				Active	Placebo	Delta	
A	**Haloperidol vs. Placebo N= 56**	48 weeks	60	11	69	58	Eklund, 1991 (10)
B	**Ziprasidone vs Placebo (Figure 1A) N=294**	52 weeks	40	43	77	34	Arato, 2002 (7)
			60	35		42	
			180	36		41	
C	**Ziprasidone vs. Placebo N=294**	52 Weeks	20	41	71	30	NDA Statistical Review
			40	35		36	
			80	36		35	
		28 Weeks	20	34	55	21	
			40	33		22	
			80	32		23	
D	**Olanzapine vs. Placebo N= 58**	46 weeks	12.1	29	70	41	Dellva, 1997 (9)
E	**Olanzapine vs. Placebo (Figure 1C) N= 326**	26 weeks	10-20	6	55	49	Beasley, 2003 (8)
F	**Aripiprazole vs. Placebo (Figure 1B) N=297**	26 week	15	39	63	24	Pigott, 2003 (12)

An additional interesting observation is made when relapse data from placebo-controlled, long-term efficacy studies are compared. Among active treatments, relapse occurred predominately at the beginning of the study period (before 6 months of treatment). In contrast, placebo relapse occurred at a steady rate throughout the 12-month period of the study (7-10, 12). This difference in relapse over time is exemplified by the Ziprasidone Extended Use in Schizophrenia (ZEUS) study (Figure 1) (7). In total, 34% (71/206) of ziprasidone-treated patients relapsed during the study. Of these, the vast majority of relapses among ziprasidone patients (61/71; 86%) occurred in the first 6 months of the study, while only 9/71 (14%) cases of relapse occurred in the second 6 months of the study.

This pattern of relapse for antipsychotics, where rates are highest in the first 6 months of the study, and much lower in the second 6 months, has been observed outside of the context of placebo-controlled study designs. We have observed relapse rates over time for haloperidol and iloperidone, an atypical antipsychotic in development, that are similar to that of the active arm in the ZEUS study (unpublished results). This finding is consistent with other active-control studies (13-17) and suggests that the biphasic relapse seen with antipsychotics does not depend on the presence of a placebo.

Distinct Margin of Separation

The second condition is that the margin of separation must not be larger than the difference between the active control drug and placebo. The studies discussed above provide the information needed to define the margin of difference between placebo and actives in long-term assessments of antipsychotic efficacy. Based on data in Table 1, it can be concluded that a margin of separation between active and test drug in an active-control trial must be at least < 27%.

Conclusion

Both placebo- and active-control study designs offer advantages and disadvantages. Active-control studies are commonly criticized for assay sensitivity: if the test drug is found to be non-inferior to the comparator, it cannot be determined if both drugs failed or succeeded. However, existing data demonstrate that antipsychotics separate consistently and significantly from placebo. The ICH E10 Guidance (3) advises that assay sensitivity can be deduced from historical evidence available from similarly designed trials is available.

Placebo-controlled studies are often deemed valid because they offer assay sensitivity. However, in the context of long-term assessments of anti-psychotic effectiveness, placebo controls may introduce biases that effectively unblind treatment. The impact of this unintended unblinding is that bias is introduced, as referenced in ICH E-10 (3). E-10 instructs that the "placebo-controlled trial, using randomization and blinding, generally minimizes subject and investigator bias. Such trials, however, are not impervious to blind-breaking through recognition of pharmacologic effects of one treatment; blinded outcome assessment can enhance bias reduction in such cases….Subjects who sense they are not improving may withdraw from treatment because they attribute lack of effect to

having been treated with placebo, complicating the analysis of the study. With care, however, withdrawal for lack of effectiveness can sometimes be used as a study endpoint. Although this may provide some information on drug effectiveness, such information is less precise than actual information on clinical status in subjects receiving their assigned treatment."

In summary, active-control designs in the assessment of long-term antipsychotic effectiveness are valid and may offer advantages over placebo-control studies.

II. Stabilization period in studies of long-term effectiveness of antipsychotics

It has been suggested that in order to assess long-term maintenance of antipsychotic effect, a relapse prevention trial design is needed in which patients must be stabilized on the medication of interest for a "clinically meaningful period of time" prior to the relapse phase of the trial. However, consensus has not been reached on what constitutes a "clinically meaningful" period of stabilization.

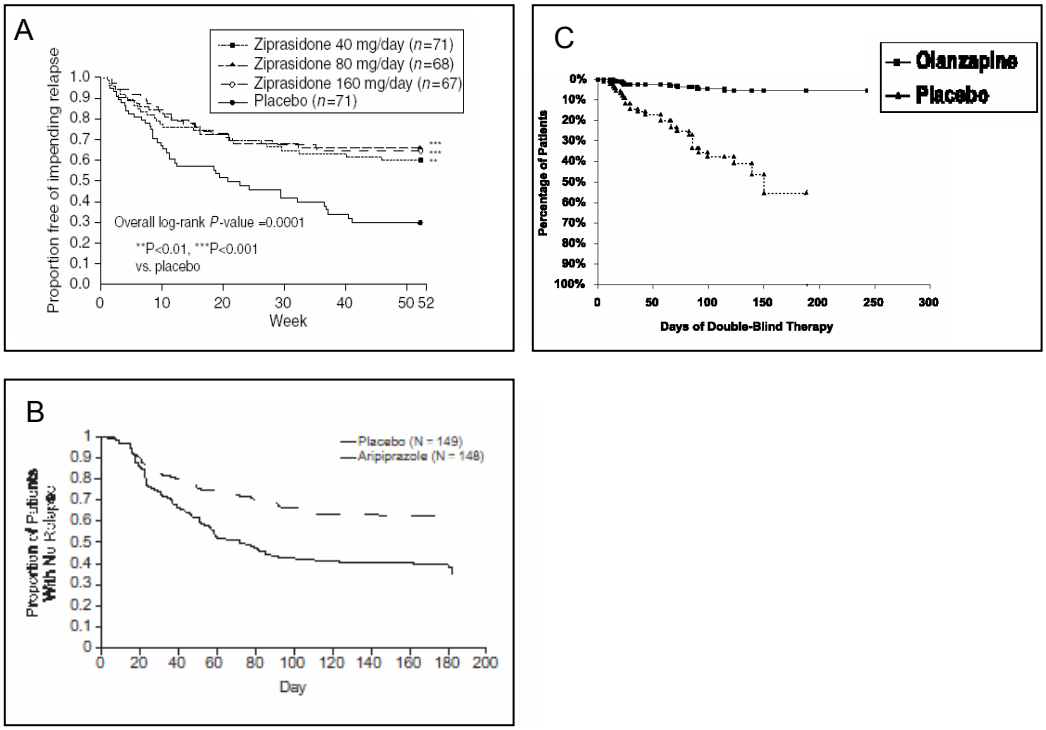
The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study is a comprehensive assessment of antipsychotic performance under conditions of standard clinical practice (18). The CATIE study compared the relative effectiveness of atypical antipsychotics olanzapine, quetiapine, risperidone and ziprasidone with the first-generation antipsychotic perphenazine. The primary aim of the study was to delineate differences in the effectiveness of these five treatments. A primary measure of effectiveness was time to discontinuation. In assessing time to discontinuation, the duration of successful treatment was also determined. On average, the antipsychotics studied treated patients successfully for 1 month (olanzapine: 3 months; quetiapine: 1 month; risperidone: 1 month; perphenazine: 1 month; ziprasidone: 1 month). Successful treatment was defined as a CGI severity score of at least 3 (mildly ill) or by a score of 4 (moderately ill) with an improvement of at least two points from baseline. Thus, in standard clinical practice, the mean duration of stabilization is relatively short. Stabilization periods that precede randomization to the withdrawal portion of a long-term effectiveness trial should not exceed the expected duration of successful management of schizophrenic symptoms.

III. Conclusions

To assess appropriate design of long-term studies of antipsychotic efficacy, historical data and current practices were reviewed. Several conclusions can be made. First, active-control trial designs are valid for the examination of long-term antipsychotic effectiveness. Existing data confirm that this trial design has assay sensitivity. Secondly, lengthy stability periods preceding the withdrawal phase of long-term maintenance studies do not reflect current clinical practice. Introduction of lengthy stability periods ($\geq$ 6 months) would not be expected to contribute to the clinical meaningfulness of such studies.

Figure 1 Proportion of patients relapsing during long-term treatment with atypical anti-psychotic medication or placebo

(A) Kaplan Meier estimate of time to relapse for ziprasidone vs. placebo (7). (B) Kaplan-Meier estimate of time to relapse for Aripiprazole vs. placebo (12). (C) Kaplan Meier estimate of time to relapse for olanzapine vs. placebo (8).



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